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REGISTRERINGSVERKET • PATE

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For the Patent- and Registration Office

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Avgift
Fee 170:-

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SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

NOVEL LACTAMS AND USES THEREOF

Field of the invention

The present invention relates to novel lactams, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of various diseases especially Alzheimer's disease and other diseases relating to the deposition of amyloid.

Background of the invention

Alzheimer's Disease (AD) is a progressive, neurodegenerative disease characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotionally stability. AD is a common cause of dementia in humans and a leading cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major public health problem throughout the world. No treatment that effectively prevents AD or reverses the clinical symptoms and underlying pathophysiology is currently available and the disease is currently considered among experts to be incurable.

The histopathological manifestations of AD are characteristic lesions known as amyloid (or senile) plaques and neurofibrillar tangles that are found in the regions of the brain associated with memory, reasoning and cognition. Similar alterations are observed in patients with Trisomy 21 (Down's syndrome) and hereditary cerebral hemorrhage with amyloidosis of the Dutch-type.

The major constituent of amyloid plaques is amyloid β protein. Amyloid β protein is derived from the proteolytic cleavage of amyloid precursor protein (APP). Processing of APP to amyloid β protein and other APP fragments is governed by a group of enzymes known as secretases. One type of secretase, γ-secretase, is responsible for the protein cleavage that produces amyloid β protein. Compounds that inhibit either β or γ secretase activity, either directly or indirectly would reduce the production of amyloid β protein resulting in the treatment or prevention of disorders associated with amyloid β protein. Thus there is a continuing need for compounds

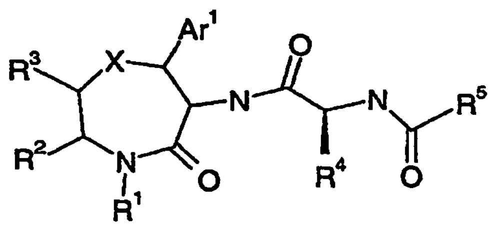
that inhibit amyloid β protein production. The present invention meets this and related needs by providing a family of novel compounds and related methods of use.

Summary of the invention

In accordance with the present invention, the applicants have hereby discovered novel compounds that inhibit γ secretase and thereby inhibit the production of amyloid β protein. The invention includes pharmaceutically acceptable salts or prodrugs of such compounds. Also in accordance with the present invention applicants provide pharmaceutical compositions and a method to use invention compounds in the treatment of degenerative neurological disorders.

Detailed description of the invention

Provided herein are novel compounds of structural diagram (I):



wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 2 sulfur atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, 2 or 3 R^c;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5 or 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or substituted phenyl with 0, 1, 2, or 3 R^e;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, C_{1-3}alkoxy, or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, aryl, or heteroaryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, SH, CH_2SCH_3, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, 2 or 3 R^e;

R^{10} is alkyl or R^9;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention occurs wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, or NR^aR^b;

R^e is, at each occurrence independently selected from OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-3}alkyl, or C_{1-3}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, or aryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_1-3alkyl, or C_1-3alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl or aryl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, NO_2, F, Cl, Br, I, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, or 1 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3, C_{1-6}alkyl;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, or 2 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, NO_2, CF_3, or C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from C_{1-6}alkyl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

Another embodiment of the invention occurs wherein:

X is C, O, SO_2 or S;

Ar^1 is a 6-membered aromatic or heteroaromatic ring having 0, or 1 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CF_3;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, or CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, or OH;

R^9 is phenyl substituted with 2 R^e;

R^{10} is R^9;

Another embodiment of the invention occurs wherein X is C, O, SO_2 or S.

Another embodiment of the invention occurs wherein:

Ar^1 is a 5-or 6-membered aromatic or heteroaromatic ring optionally substituted with 0 or 1 R^e said ring having 1 nitrogen, oxygen or sulfur atom.

Another embodiment of the invention occurs wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b.

Another embodiment of the invention occurs wherein:

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl.

Another embodiment of the invention occurs wherein:

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f.

Another embodiment of the invention occurs wherein:

R^e is, at each occurrence independently selected from F or Cl.

Another embodiment of the invention occurs wherein R^f is F or Cl.

Another embodiment of the invention occurs wherein R^4 is H or CHR^7R^8.

Another embodiment of the invention occurs wherein R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$.

Another embodiment of the invention occurs wherein:

R^7 and R^8 are, at each occurrence independently selected from H or OH.

Another embodiment of the invention occurs wherein R^9 is phenyl substituted with 2 R^e.

Another embodiment of the invention occurs wherein R^{10} is phenyl substituted with 2 R^e.

Another embodiment of the invention occurs wherein:

X is C, O, SO_2 or S;

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b;

R^a and R^b are, at each occurrence independently selected from H,or C_{1-4}alkyl;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0,1 or 2 R^f;

R^e is, at each occurrence F;

R^f is F or Cl;

R^4 is H, or CHR^7R^8;
R^5 is C_{1-3}alkylR^9 or CH(OH)R^{10};
R^7 and R^8 are, at each occurrence independently selected from H or OH;
R^9 is phenyl 3, 5-disubstituted with F;
R^{10} is phenyl 3, 5-disubstituted with F.

In a further embodiment the present invention provides a compound selected from:
(2S)-N-[(2S,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2R,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2S,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-N-[(2R,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3S)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3S)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2R,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;

(2*S*)-*N*-[(2*S*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2*R*,3*R*)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2,3-*cis*)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2,3-cis)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(*6RS,7RS*)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]propanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3,4-*cis*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-Difluorophenyl)acetyl]-N^1-[(3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-terahydro-1H-1-benzazepin-3-yl]-L-alaninamide

or a pharmaceutical acceptable salt thereof.

The use of a compound as defined herein, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with β-amyloid production, Alzheimer's disease, or Down's Syndrome.

A method for the treatment of neurological disorders associated with β-amyloid production comprising administering to a host in need of such treatment a therapeutically effective amount of a compound as defined herein.

A method for inhibiting γ-secretase activity comprising administering to a host in need of such inhibition a therapeutically effective amount of a compound as defined herein that inhibits γ-secretase activity.

A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising adminstering a therapeutically effective amount of a compound as defined herein.

A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising adminstering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt as defined herein.

A pharmaceutical composition comprisisng a compound of formula (I), as defined herein, together with at least on phamraceutically acceptable carrier, diluent or excipent.

Definitions

The definitions set forth in this section are intended to clarify terms used throughout this application. The term "herein" means the entire application.

As used in this application, the term "substituted," as used herein, means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. For example when a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^1, R^7, R^a, R^e etc.) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^1, then said group may optionally be substituted with 0,1, 2 or 3 R^1 groups and R^e at each occurrence is selected independently from the definition of R^e. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. When required, separation of the racemic material can be achieved by methods known in the art. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein "acyl" refers to radicals of the of the general formula –C(=O)-R, wherein R is hydrogen, hydrocarbyl radical, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

As used herein "aromatic" refers to hydrocarbyl radicals having one or more polyunsaturated carbon rings having aromatic character, (e.g., 4n + 2 delocalized electrons) and comprising up to about 14 carbon atoms.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. As used herein, "C_{1-3} alkyl", whether a terminal substituent or an alkylene group linking two substituents, is understood to specifically include both branched and straight-chain methyl, ethyl, and propyl.

As used herein, "alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration with one or more unsaturated carbon-carbon bonds that may occur at any stable point along the chain. Examples of "C_{3-6}alkenyl" include, but are not limited to, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, hexenyl, and the like.

As used herein, "alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration with one or more carbon-carbon triple bonds that may occur at any stable point along the chain, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like.

As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Preferred alkoxy

groups are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy. Similarly, "alkylthio" or "thioalkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the term "aryl" is intended to mean aromatic radicals including both monocyclic aromatic radicals comprising 6 carbon atoms and polycyclic aromatic radicals comprising up to about 14 carbon atoms.

As used herein, "carbocycle" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, bicyclooctane, bicyclononane, bicyclodecane (decalin), bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. For example, "C_{3-6} cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein "cycloalkenyl refers to ring-containing radicals having at least one carbon-carbon double bond in the ring, and having in the range about 3 up to 12 carbons atoms.

As used herein "cycloalkynyl" refers to ring-containing radicals having at least one carbon-carbon triple bond in the ring, and having in the range about 3 up to 12 carbons atoms.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -- C_vF_w where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not

limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, heptafluoropropyl, and heptachloropropyl. "Haloalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge; for example trifluoromethoxy, pentafluoroethoxy, 2,2,2-trifluoroethoxy, and the like. "Halothioalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the term "heterocycle" or "heterocyclic" refersto a ring-containing monovalent and divalent radicals having one or more heteroatoms, independently selected from N, O and S, as part of the ring structure and comprising at least 3 and up to about 20 atoms in the rings. Heterocyclic groups may be saturated or unsaturated, containg one or more double bonds, and heterocyclic groups may contain more that one ring. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, nitrogen in the heterocycle may optionally be quaternized. It is understood that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H, 6H-1, 5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1, 2,5-thiadiazinyl, acridinyl, azetidine, aziridine, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dioxolane, furyl, 2,3-dihydrofuran, 2,5-dihydrofuran, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, homopiperidinyl, imidazolidine, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxirane, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,

phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, purinyl, pyranyl, pyrrolidine, pyrroline, pyrrolidine, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, N-oxide-pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, thiophane, thiotetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, thiirane, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

As used herein, "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional

chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers that release the active parent drug according to formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

Formulation

Compounds of formula I according to the present invention may be administered orally, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

Preferred routes of administration are orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the

attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

An effective amount of a compound of formula I of the present invention for use in therapy of Alzheimer's Disease is an amount sufficient to symptomatically relieve in a warm-blooded animal, particularly a human the cognitive symptoms, to slow the progression of worsening cognitive symptoms, or to reduce in patients with cognitive symptoms the risk of getting worse (progressing to dementia or worsening the present degree of dementia).

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers include magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Salts include, but are not limited to, pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts of compounds of the present invention include: acetate, bicarbonate, carbonate, hydrobromide, hydrochloride, phosphate/diphosphate, sulfate, choline, diethanolamine, ethylenediamine, meglumine, aluminum, calcium, magnesium, potassium and sodium.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is

thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

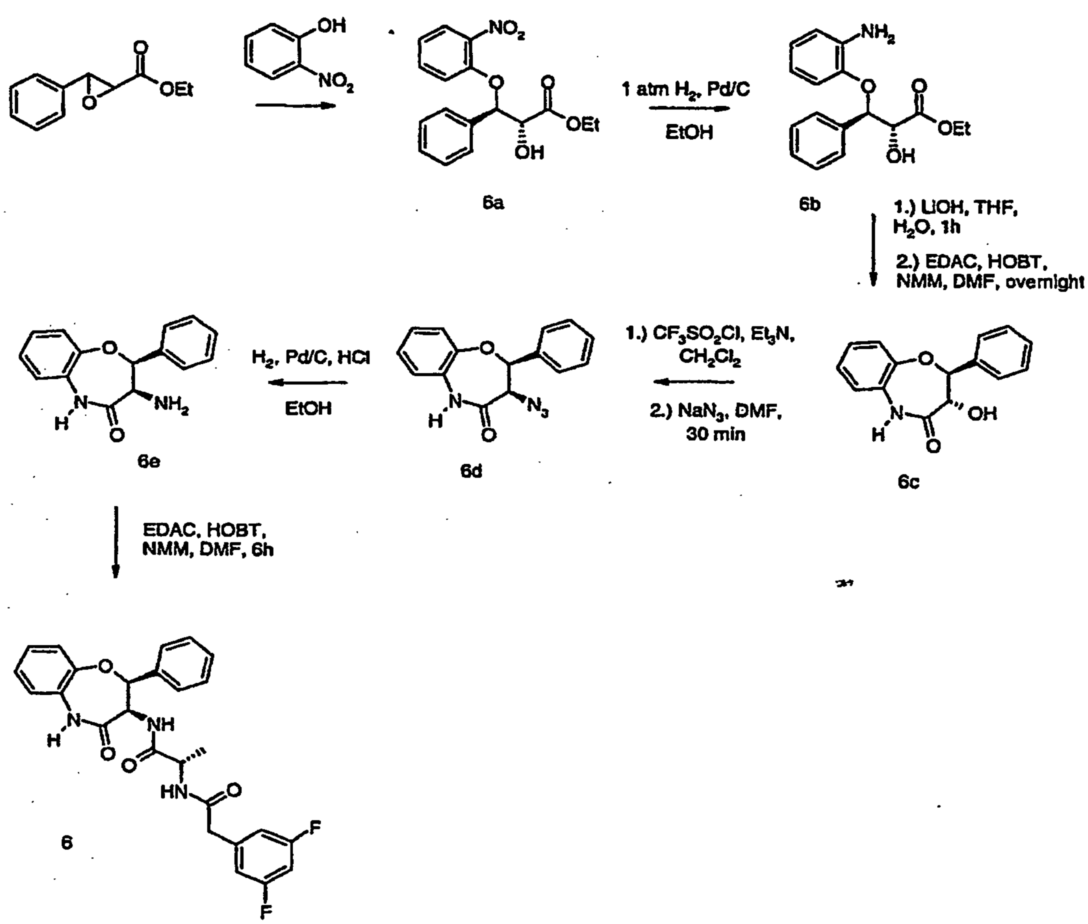
Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Such methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this application. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the

transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

An example of such a process is illustrated herein.



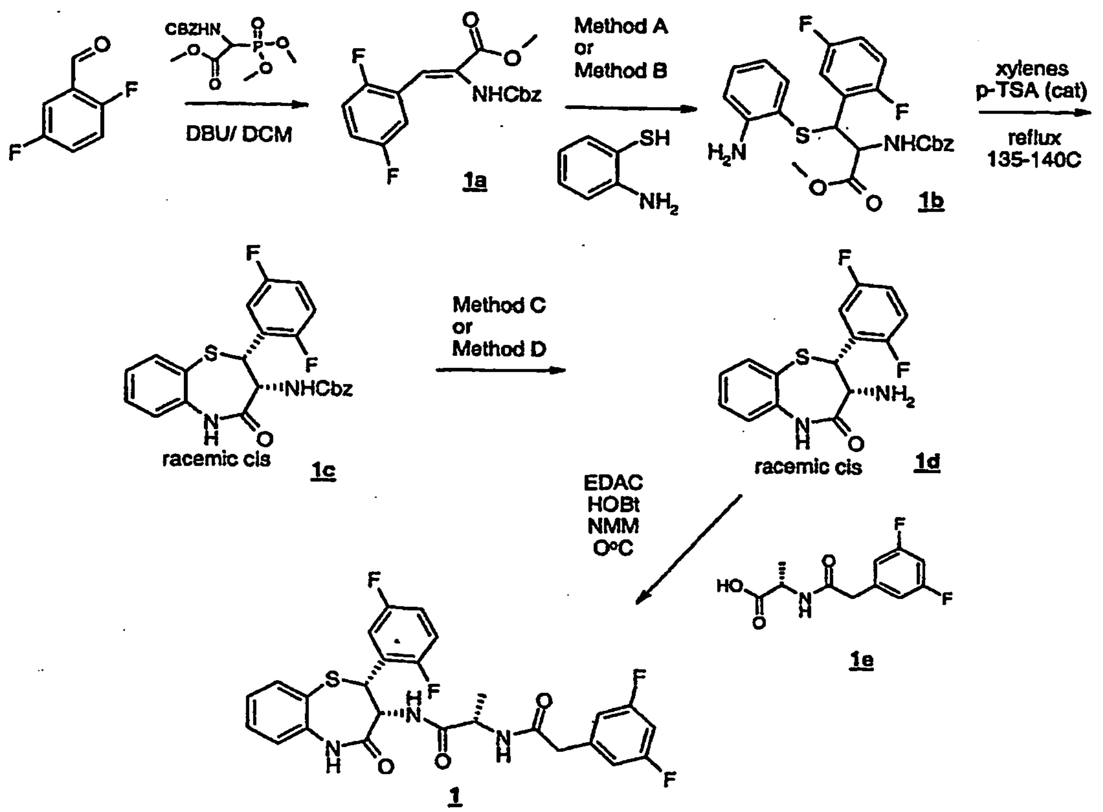
Examples

Chemical abbreviations used in the Examples are defined as follows: "BOC" denotes N-tert-butoxycarbonyl, "CBZ" denotes carbobenzyloxy; "DBU" denotes 1,8-diazabicyclo[5.4.0]undec-7-ene; "DMF" denotes N, N-dimethylformamide; "EDAC-HCl" denotes 1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride; "HOBt" denotes hydroxybenzotriazole; "NMM" denotes N-methylmorpholine; "p-TSA" denotes p-toluenesulfonic acid "TBAB" denotes tetrabutylammonium bromide; "THF" denotes tetrahydrofuran, Tos-Cl denotes p-toluenesulfonyl chloride, "min." denotes minutes; "h" denotes hours; "RT" denotes room temperature. Unless otherwise noted, organic solutions were "dried" over anhydrous sodium sulfate.

HPLC Method A: Phenomenex Luna 3μ C18(2), 4.6 x 75mm column. Solvents: A = H_2O with 0.1% TFA, B = Acetonitrile with 0.1% TFA. Flow rate 2.0 mL/min. 20% B until 0.5 min then a linear gradient to 95% B at 3 min. Maintain at 95% B until 6 min

LC/MS HPLC method: Agilent Zorbax 5μ SB-C8 column 2.1mm x 5 cm. Solvents: A = H_2O with 0.05% TFA, B =10% H_2O, 90% Acetonitrile, 0.05% TFA. Gradient: (10-90%B over 3 min., 90% B hold thru 4 min., -10% B at 5 min. and hold at 10% B until 6 min).

Example 1



Example 1. ***N*²-[(3,5-difluorophenyl)acetyl]-*N*¹-[(2*R*,3*R*)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide (1)**

To a solution of racemic 2,3-*cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (1d) (300mg) in dichloromethane (40mL) at 0°C under N_2 was added *N*-[(3,5-difluorophenyl)acetyl]-L-alanine (1e) (238 mg), HOBt-hydrate (330 mg), EDAC-HCl (282 mg) and N-methyl morpholine (165 mg). The reaction mixture was stirred 1 H at 0°C, concentrated in vacuo and partitioned between water (100mL) and ethyl acetate (125mL). The organic phase was collected and consecutively washed with water, saturated aqueous sodium bicarbonate, and brine, dried , filtered and evaporated to yield a mixture of the title compound and *N*²-[(3,5-difluorophenyl)acetyl]-*N*¹-[(2*S*,3*S*)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide. The crude product (500 mg) was purified by flash chromatography (50%ethyl acetate/hexanes) to afford the title compound (180mg, 69%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 3H), 3.48 (s, 2H), 4.29 (p, 1H), 4.93 (t, 1H), 5.68 (d, 1H), 6.01 (d, 1H), 6.50 (d, 1H), 6.73-6.80

(m, 3H), 6.93-7.02 (m, 2H), 7.15 (d, 1H), 7.30 (t, 1H), 7.43 (t, 1H), 7.5-7.6 (m, 1H), 7.73 (d, 1H), 7.74 (s, 1H). MS APCI, m/z = 532(M^+). LC/MS: 2.53 min., Method A. The starting amine, racemic 2,3-*cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (<u>1d</u>), was prepared in the following manner:

<u>a. Methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-(2,5-difluorophenyl)prop-2-enoate</u> (<u>1a</u>). A stirred solution of N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (6.1 g) and 2,5-difluorobenzaldehyde (2.0 g) in dry dichloromethane (60 mL), was treated dropwise with a solution of DBU (2.5mL) in dichloromethane (20 mL). The mixture was stirred at room temperature for 2h, then was concentrated to approximately 20 mL and partitioned between ethyl acetate (150 mL) and 1N hydrochloric acid (50 mL). The organic extract was collected, consecutively washed with 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate, and brine, dried (sodium sulfate), filtered and evaporated. The crude product (6.5g) was purified by flash chromatography (20%ethyl acetate/hexanes) to yield the title compound (4.0g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.10, (s, 2H), 6.60 (bs, 1H), 6.9-7.1 (m, 2H), 7.21 (m, 1H), 7.2-7.3 (m, 6H). MS APCI, m/z = 348(M^+). LC/MS: 2.53 min (Method A).

<u>b. Methyl β-[(2-aminophenyl)thio]-*N*-[(benzyloxy)carbonyl]-2,5-difluorophenylalaninate</u> (<u>1b</u>).

<u>Method A</u>

To an ice-cooled solution of sodium methoxide (760 mg) in anhydrous methanol (20 mL) under N_2 (vacuum degassed 3x with nitrogen) was added 2-aminothiophenol (1.7 g). The reaction mixture stirred at 0° C for 10 min and then a solution of methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-(2,5-difluorophenyl)prop-2-enoate (2.32 g) in methanol (10 mL) was added. The reaction mixture was heated to reflux for 2h and then was cooled to room temperature and stirred overnight. The reaction mixture was concentrated to ca. 10 mL, then was partitioned between cold 1N hydrochloric acid (75 mL) and ethyl acetate (125 mL). The organic phase was separated and consecutively washed with 1N hydrochloric acid (4x), dilute aqueous sodium bicarbonate and brine, dried , filtered and evaporated. The title compound was isolated as the hydrochloride salt. (3.0g, 88 %, 2:1 Z:E). ^{1}H NMR (300 MHz, d6-DMSO) δ 3.4 (s, 2H), 3.7 (s, 1H), 4.6–5.1 (m, 7H), 6.3 (t, 0.67H), 6.4 (t, 0.33H), 6.7-

7.4 (m, 10H), 8.1 (d, 0.33H),), 8.4 (d, 0.67H). MS APCI, m/z = 473(M^+). LC/MS: 2.78 min.

Method B

To an ice-cooled solution of 2-aminothiophenol (8.7g) in anhydrous methanol under N_2 (vacuum degassed 3x with nitrogen) was added methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-(2,5-difluorophenyl)prop-2-enoate (3.46 g) followed by triethylamine (975uL). The reaction mixture was stirred at room temperature for 4 days, then was reduced in vacuo to near dryness. The mixture was partitioned between cold 1N hydrochloric acid (75 mL) and ethyl acetate (125 mL). The organic phase was separated and consecutively washed with 1N hydrochloric acid (4x), dilute aqueous sodium bicarbonate and brine, dried, filtered and evaporated to yield 5.8 g of an oil. Purification by flash chromatography (25 % ethyl acetate/hexanes) afforded the title compound (4.3g, 65%) Z:E ratio of 82:18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 2.4H), 3.71 (s, 0.6H), 4.28 (s, 1.6H), 4.72 (s, 0.4H, 4.8–5.1 (m, 4H), 5.3 (d, 0.2H), 5.86 (d, 0.8H), 6.58 (t, 0.8H), 6.68 (d, 0.8H), 6.9-7.4 (m, 8H). MS APCI, m/z = 473(M^+). LC/MS: 2.78 min.

c. **Benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (1c).**

A suspension of methyl β-[(2-aminophenyl)thio]-*N*-[(benzyloxy)carbonyl]-2,5-difluorophenylalaninate (4:1, Z:E) (4.3 g) and p-toluenesulfonic acid (catalytic) in xylenes (100 mL) was heated to reflux for 2 h, using a Dean-Stark apparatus to remove water. The mixture was then cooled, resulting in precipitation of the crude product as a white solid (3.3 g, 4:1, cis:trans). This was recrystallized from ethyl acetate/ether to afford the title compound (2.4 g, 60 %). ^{1}H NMR (300 MHz, d6-DMSO) δ 4.63 (t, 1H), 4.96 (s, 2H), 5.47 (d, 1H), 7.00 (d, 1H), 7.23–7.34, (m, 9H), 7.49-7.53 (m, 2H), 7.70 (d, 1H), 10.57 (s, 1H). MS APCI, m/z = 441(M^+). LC/MS: 2.74 min.

d. ***cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (1d)**

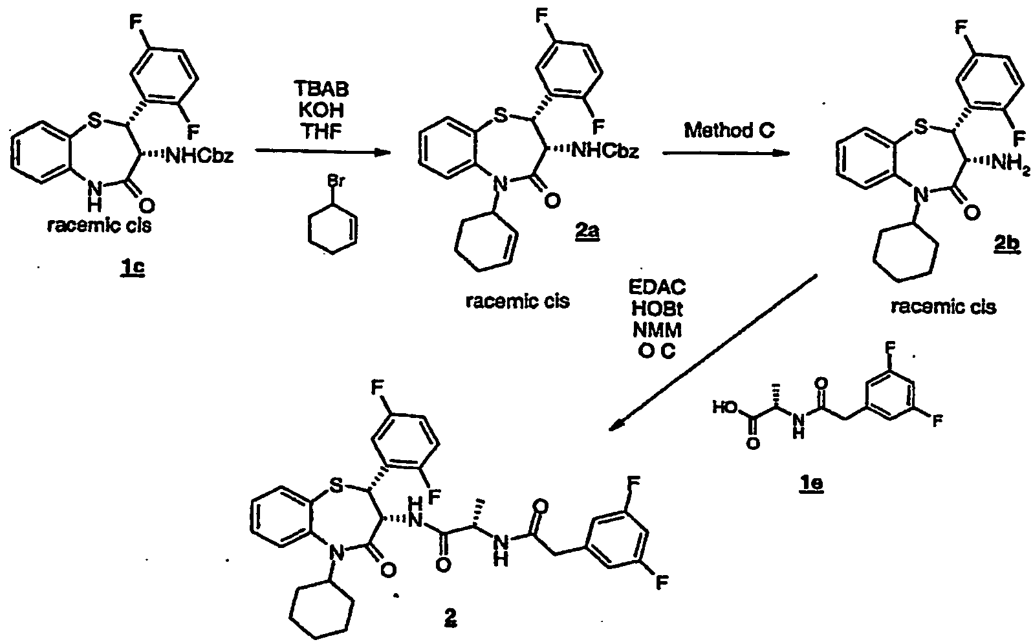
Method C

A mixture of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (1.7 g) and 10% palladium on carbon (1.7 g, DeGussa type 50%wt water) in glacial acetic acid (80 mL) was hydrogenated at 50 psi H_2 for 3h. The reaction mixture was filtered through Celite and concentrated in vacuo. The crude oil was triturated with ether to yield a white solid (1.3g). The solid was partitioned between ethyl acetate and dilute ammonium hydroxide. The organic phase was separated and consecutively washed with dilute ammonium hydroxide and brine, dried and evaporated. The residue was treated with saturated HCl(g) in ethyl aceate/ether to provide the hydrochloride salt of the title compound as a white solid (1.1g, 90%). ^{1}H NMR (300 MHz, d6-DMSO) δ 4.33 (d, 1H, J=7 Hz), 5.6 (d, 1H, J=7 Hz), 7.13–7.38 (m, 4H), 7.48-7.60 (m, 2H), 7.72, (d, 1H), 8.4 (bs, 3H), 11.0 (s, 1H). MS APCI, m/z = 307(M^+). LC/MS: 1.65 min.

Method D

To benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (0.9 g) was added 30 % HBr/HOAc (5mL). The stirred suspension became a homogeneous solution over 20 min. The reaction stirred at room temperature for an additional 50 min, then was diluted with ether to afford the hydrobromide salt of the title compound (0.75g, 95%). The solid was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separatated and consecutively washed with dilute aqueous sodium bicarbonate and brine, dried , filtered and evaporated. The resulting oil was treated with saturated HCl(g) in ethyl aceate/ether to provide the hydrochloride salt of the title compound as a white solid (0.60 g, 85%). This material was indistinguishable to that obtained by Method C.

Example 2.



Example 2. N^1-[(2,3-*cis*)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide (2).

Using a procedure similar to that described in Example 1, except using (2,3-*cis*)-3-amino-5-cyclohexyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2b) (85mg) as the amine component, the title compound (2) was obtained as a white solid (20 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0-2.1 (m, 13H), 3.47(s, 2H), 4.2 (p, 1H), 4.45 (m, 1H), 4.64 (t, 1H), 5.44 (d, 1H), 5.95 (d, 1H), 6.40 (d, 1H), 6.73-6.80 (m, 3H), 6.85-6.95 (m, 2H), 7.35-7.49 (m, 4H), 7.75 (d, 1H). MS APCI, m/z = 614(M^+). LC/MS: 3.44 min.

The amine component, (2,3-*cis*)-3-amino-5-cyclohexyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2b) was prepared in the following manner:

a. **Benzyl (2,3-*cis*)-5-(2-cyclohexen-1-yl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 2a**

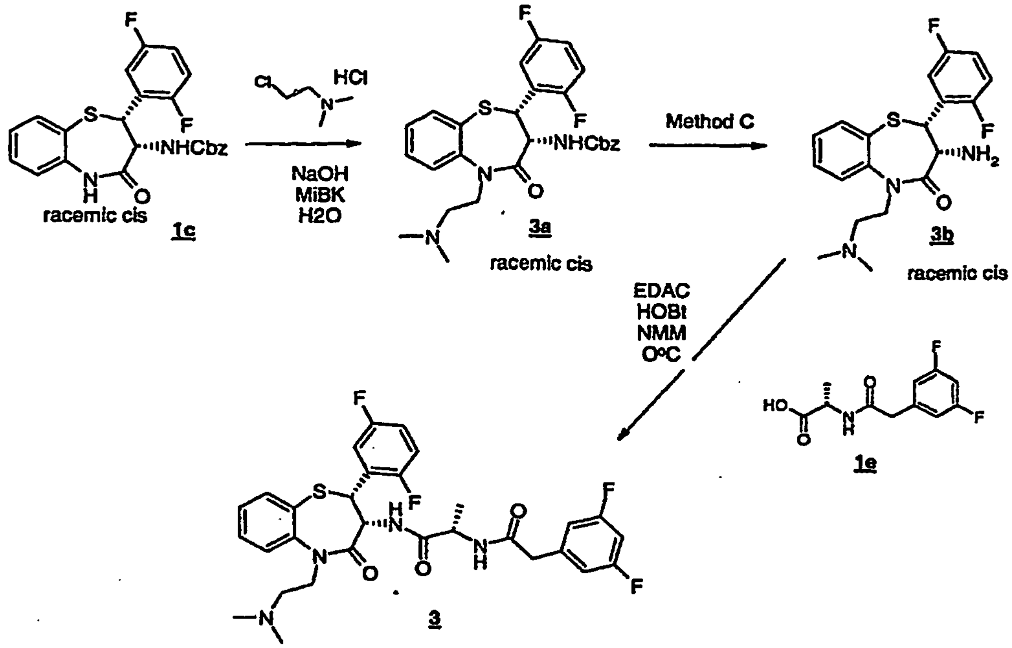
To a solution of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 1c (150 mg,), prepared as described in Example 1, part

c, in THF (10 mL) under N_2 was added powdered potassium hydroxide (25 mg), tetrabutylammonium bromide (11 mg) and 1-bromo-2-cyclohexene (40μl). The reaction mixture was stirred at RT overnight, then was partitioned between water and ethyl acetate. The organic phase was separated and consecutively washed with water and brine, dried , filtered and evaporated to yield the title compound 2a (175 mg, 98%). This material was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5-2.3 (m, 6H), 4.6 (t, 1H), 5.0 (d, 2H), 5.2–5.5,(m, 3H), 5.7 (m, 1H), 5.9 (m, 1H), 6.9 (m, 2H), 7.2-7.3 (m, 6H), 7.4 (m, 3H), 7.73 (d, 1H). MS APCI, m/z = 521(M^+). LC/MS: 3.63 min

b. **(2,3-*cis*)-3-amino-5-cyclohexyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2b).**

Using a method similar to that described in Example 1, part d (Method C), benzyl (2,3-*cis*)-5-(2-cyclohexen-1-yl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 2a (90mg) was converted to crude 2b. The crude product purified by flash chromatography (2%MeOH, 1% $NH_4OH/CHCl_3$) to yield 2b (45mg, 67%), converted to HCl salt (EtOH/ether/HCl). ^{1}H NMR (300 MHz, d6-DMSO) δ1.0-2.1 (m, 10H), 4.11(d, 1H), 4.35 (m, 1H), 5.38 (d, 1H), 7.35 (t, 2H), 7.4–7.5 (m, 2H), 7.6-7.7 (m, 2H), 7.81, (d, 1H), 8.29 (bs, 3H). MS APCI, m/z = 389(M^+). LC/MS: 2.57 min.

Example 3.



Example 3. N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide (3)

Using a procedure similar to that described in Example 1, except using racemic (2,3-*cis*)-3-amino-2-(2,5-difluorophenyl)-5-(2-dimethylamino)ethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (3b) (100 mg) as the amine component, the title compound (3) was obtained as a white solid (37 mg, 46%). ^{1}H NMR (300 MHz, d6-DMSO) δ1.2 (3H), δ2.3(s, 6H), δ2.35 (m, 1H), δ2.6,(m, 1H), δ3.48 (s, 2H),), δ3.55 (m, 1H),), δ4.22 (p, 1H),), δ4.65 (m, 1H), δ4.77 (t, 1H),), δ5.53 (d, 1H),), δ5.95 (d, 1H),), δ6.36 (d, 1H), δ6.7–7.0 (m, 5H), δ7.27–7.35 (t, 1H), δ7.38 (d, 1H), δ7.48, (t, 1H), δ7.71 (d, 1H), δ7.9 (m, 1H),. MS APCI, m/z = 603(M$^+$). LC/MS: 2.13 min.

The amine component, (2,3-*cis*)-3-amino-5-(2-dimethylamino)ethyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (3b) was prepared in the following manner:

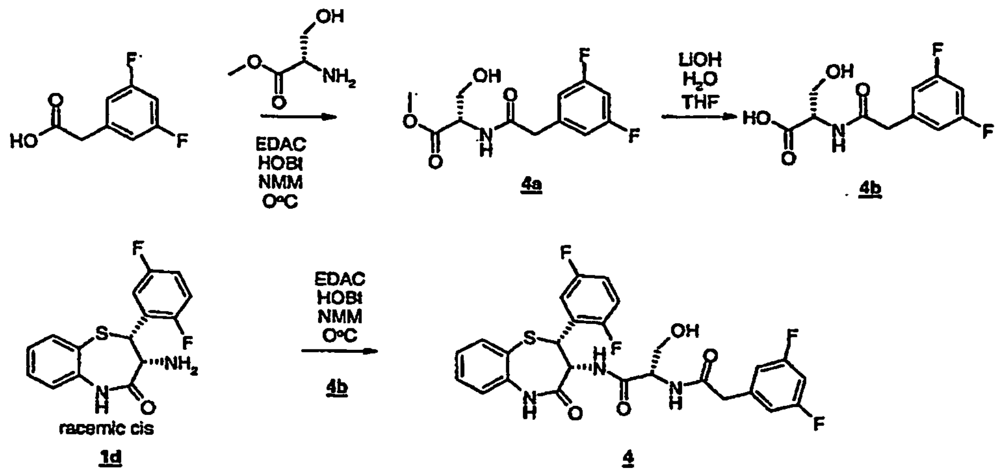
a. **Benzyl (2,3-*cis*)-5-(2-dimethylamino)ethyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (3a)**

To a solution of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 1c (530 mg), prepared as described in Example 1, part c, in methyl isobutyl ketone (14 mL) was added 10N NaOH (0.6mL) followed by water (2.3 mL) and N, N-dimethylaminoethylchloride hydrochloride (260 mg). The reaction mixture was heated to 95° C for 4 H. (HPLC indicated 3:1 3a:1c), allowed to cool to RT and diluted with ethyl acetate. The organic phase was collected and consecutively washed with water (3X), brine, dried , filtered and the solvent removed in vacuo to yield crude oil. The crude oil was purified by flash chromatography (5%MeOH/$CHCl_3$) to afford pure title compound (400 mg, 60%). ^1H NMR (300 MHz, d6-DMSO) δ2.2 (d, 6H), δ2.3 (m, 1H), δ2.4 (m, 1H), δ3.27 (m, 1H), δ3.6,(d of t, 1H), δ4.4 (t, 1H), δ4.5 (t, 1H), δ4.9 (s, 2H), δ5.3 (d, 2H), δ6.8 (d, 1H), δ7.2–7.3 (m, 6H), δ7.4 (t, 1H), δ7.6-7.7 (m, 2H), δ7.76, (d, 1H), δ7.86 (m, 1H). MS APCI, m/z = 512(M^+). LC/MS: 2.23 min.

b. (2,3-*cis*)-3-amino-5-(dimethylamino)ethyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (3b).

Using a method similar to that described in Example 1, part d (Method C), benzyl (2,3-cis)-5-(2-dimethylamino)ethyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate, 3a (90 mg) was converted overnight to crude 3b. The crude product was purified by flash chromatography (5% MeOH, 1% $NH_4OH/CHCl_3$) to afford pure title compound (125 mg, 57%). ^1H NMR (300 MHz, d6-DMSO) δ2.29 (s, 6H), δ2.39, (m, 1H), δ2.64,(m, 1H), δ3.62 (m, 1H), δ3.79 (d, 1H), δ4.56 (dt, 1H), δ5.27 (d, 2H), δ6.95–7.05 (m, 2H), δ7.28 (m, 1H), δ7.40 (d, 1H), δ7.72, (d, 1H), δ7.78 (m, 1H). MS APCI, m/z = 378(M^+). LC/MS: 1.23 min.

Example 4.



Example 4. (2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide (4)

To a solution *N*-[(3,5-difluorophenyl)acetyl]-L-serine (4b) (75 mg) in dichloromethane (15 mL) at 0°C under N_2, was added racemic 2,3-*cis*-3-amino-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one-HCl (1d) (100 mg) followed by the HOBt-hydrate (97 mg) and NMM (32 μL). Reaction stirred for 5 min. and then added EDAC-HCl (84 mg) and NMM (50 μL). The reaction mixture was stirred 2 H at 0°C under N_2, concentrated in vacuo and partitioned between water (100 mL) and ethyl acetate (125 mL). The organic phase was collected and consecutively washed with water, saturated aqueous sodium bicarbonate , brine, dried , filtered and evaporated to yield a mixture of the title compound and (2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide. The crude product (165 mg) was purified by flash chromatography (80% ethyl acetate/hexanes) to afford the title compound (60 mg, 73%) as a white solid. ^{1}H NMR (300 MHz, d6-DMSO) δ (d, 3H), δ3.48 (s, 2H), δ4.21 (q, 1H), δ4.74,(t, 1H), δ4.85 (bs, 1H), δ5.50 (d, 1H), δ6.93 (d, 2H), δ7.09 (m, 1H), δ7.18-7.35 (m, 4H), δ7.45-7.55 (m, 2H), δ7.71 (t, 2H), δ8.17(d, 1H), δ10.68 (s, 1H). MS APCI, m/z = 548(M^+). LC/MS: 2.34 min.

The starting acid, *N*-[(3,5-difluorophenyl)acetyl]-L-serine (4b), was prepared in the following manner:

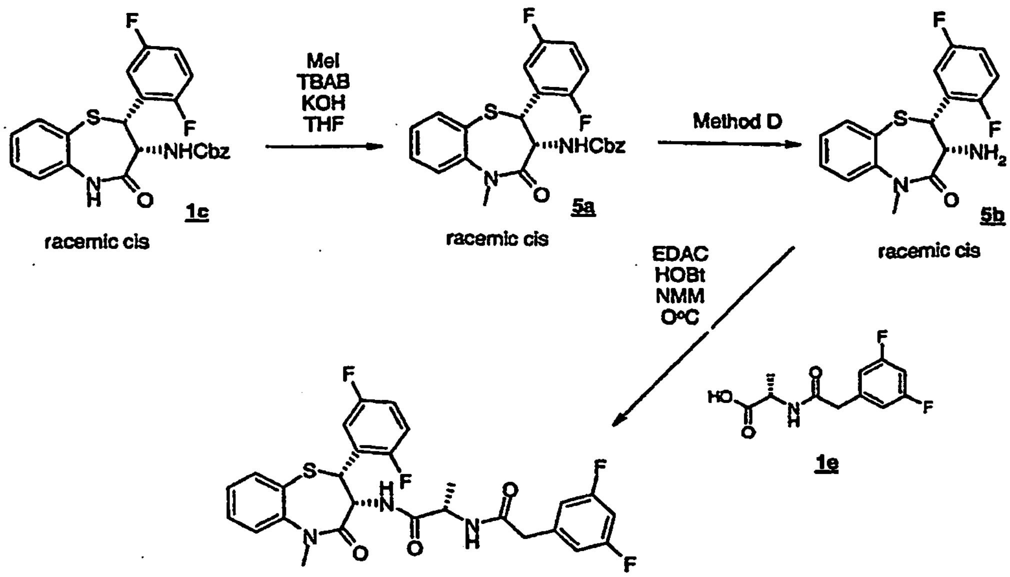
a. *N*-[(3,5-difluorophenyl)acetyl]-L-serine methyl ester (4a)

To an ice cooled solution of 3,5-difluorophenylacetic acid (2.16 g) in anhydrous dichloromethane (100 mL) under N_2 was added HOBt-hydrate (4.23 g), EDAC-HCl (3.6 g), and NMM (2.2 mL). The reaction mixture was stirred at 0°C under N_2 for 15 min and L-serine methyl ester-HCl (1.96g) was added followed by NMM (1.38 mL). The reaction was stirred at 0°C for 1 H and RT for 2 H. The reaction mixture was concentrated in vacuo and partitioned between water (100 mL) and ethyl acetate (125 mL). The organic phase was collected and consecutively washed with water, dilute aqueous sodium bicarbonate , brine, dried , filtered and the solvent removed in vacuo to yield a white solid. Trituration with $CHCl_3$ afforded pure title compound (1.8g). The impure filtrate was subjected to flash chromatography (20% acetone/$CHCl_3$) to afford additional title compound (800 mg, total yield 76%). ^{1}H NMR (300 MHz, d6-DMSO) δ3.57 (d, 2H), δ3.62(s, 3H), δ3.7 (m, 1H), δ4.35,(m, 1H), δ5.1 (bs, 1H), δ7.00 (d, 2H), δ7.09 (t, 1H), δ8.53, (d, 1H). MS APCI, m/z = 274(M^+). LC/MS: 1.34 min.

b. *N*-[(3,5-difluorophenyl)acetyl]-L-serine (4b)

To a stirred solution of *N*-[(3,5-difluorophenyl)acetyl]-L-serine methyl ester (4a) in THF (13 mL) was added 1M aqueous lithium hydroxide (13.2 mL) and the mixture stirred at RT for 40 H. Brine (50 mL) was added, the aqueous layer made acidic to pH 1 with 1N hydrochloric acid (~15 mL), and the aqueous layer extracted with 10%MeOH/ $CHCl_3$ (2X). The organic phase was collected, dried , filtered and the solvent removed in vacuo to afford the title compound (112 mg, 54 %). This material was used without further purification. ^{1}H NMR (300 MHz, d6-DMSO) δ3.57 (d, 2H), δ3.7 (m, 1H), δ4.27,(m, 1H), δ5.03 (bs, 1H), δ7.00 (d, 2H), δ7.09 (t, 1H), δ8.38, (d, 1H). δ12.6, (bs, 1H). MS APCI, m/z = 274(M^+). LC/MS: 1.0 min.

Example 5.



Example 5 N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide (5)

Using a procedure similar to that described in Example 1, except using racemic (2,3-*cis*)-3-amino-5-methyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5b) (170 mg) as the amine component, the title compound (5) was obtained as a white solid (85 mg, 59%) ^{1}H NMR (300 MHz, $CDCl_3$) δ1.19 (d, 3H), δ3.48 (s, 2H), δ3.50 (s, 3H), δ4.22 (m, 1H), δ4.83,(t, 1H), δ5.56 (d, 1H), δ5.92 (d, 1H), δ6.37 (d, 1H), δ6.8-6.9 (m, 3H), δ6.9-7.0 (m, 2H), δ7.32 (d, 1H), δ7.4-7.5 (m, 2H), δ7.72 (d, 1H). MS APCI, m/z = 546(M^+). LC/MS: 2.67 min.
The amine component (2,3-*cis*)-3-amino-5-methyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5b) was prepared in the following manner:

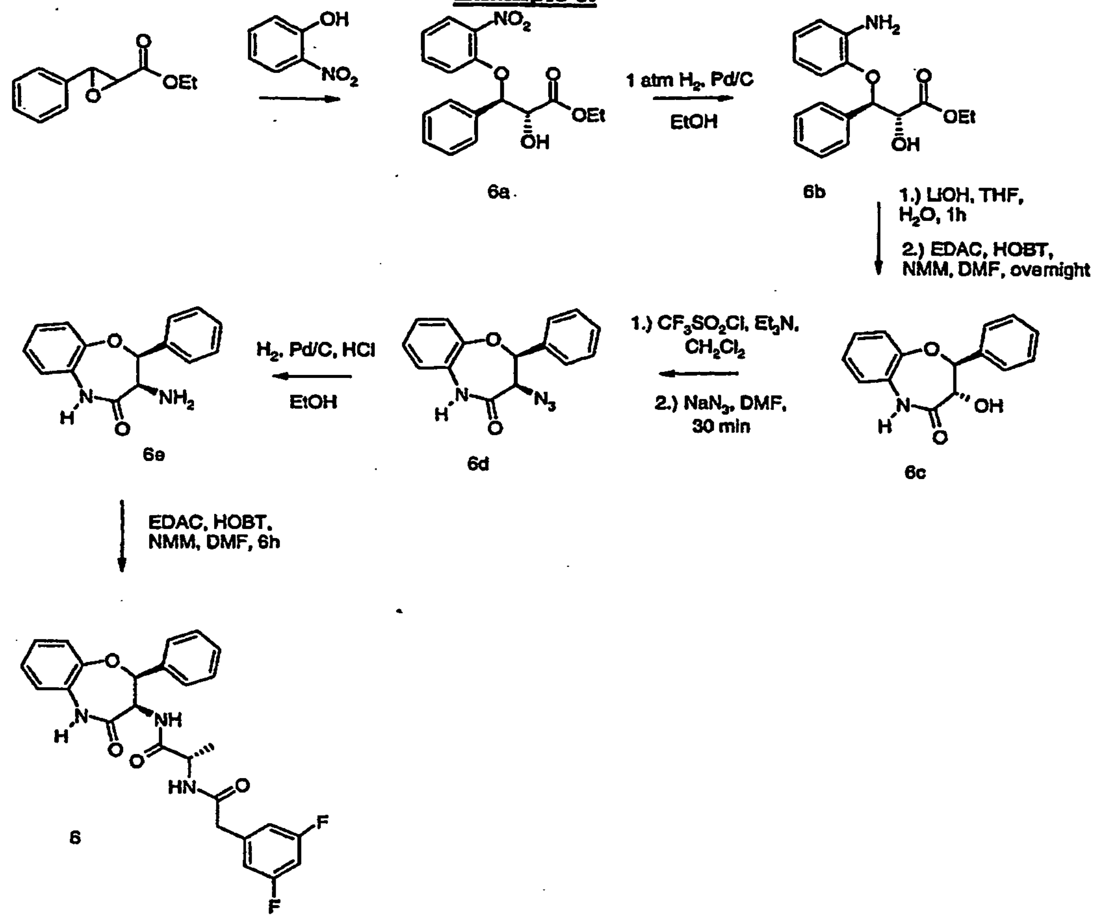
a. **Benzyl (2,3-*cis*)-5-(methyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate (5a)**
To a round bottom flask charged with powdered KOH (182 mg) under N_2 was added a solution of benzyl *cis*-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 1c (1.1 g) prepared as described in Example 1, part c,

in THF (15 mL). To the suspension was added tetrabutylammonium bromide (80 mg) followed by addition of methyl iodide (156 μl) via syringe. The mixture stirred at RT over the weekend. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was collected and consecutively washed with water and brine, dried , filtered and the solvent removed in vacuo to afford the crude product (1.15 g). Recrystallization from ethyl acetate (10 mL) yielded pure title compound 5a (660 mg, 58%). ^{1}H NMR (300 MHz, d6-DMSO) δ3.42 (s, 3H), δ4.60 (t, 1H), δ4.93 (s, 2H), δ5.34 (d, 1H), δ7.01 (d, 1H), δ7.22–7.34 (m, 7H), δ7.42 (q, 2H), δ7.62 (s, 1H), δ7.63 (d, 1H), δ7.76 (d, 1H). MS APCI, m/z = 455(M$^+$). LC/MS: 2.93 min.

b. (2,3-*cis*)-3-amino-5-methyl-2-(2,5-difluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5b).

Using a method similar to that described in Example 1, part d (Method D), benzyl (2,3-*cis*)-5-(methyl)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylcarbamate 5a (600mg) was converted to nearly pure 5b (350 mg, 83%). Recrystallization (ether/hexanes) afforded the pure title compound (162 mg). ^{1}H NMR (300 MHz, d6DMSO) δ1.6-2.5 (bs, 2H), δ3.41 (s, 3H), δ3.50 (s, 3H), δ3.76 (d, 1H), δ5.17 (d, 1H), δ7.25–7.38 (m, 4H), δ7.58 (s, 1H), δ7.59 (d, 1H), δ7.72 (d, 1H). MS APCI, m/z = 321(M$^+$). LC/MS: 1.76 min.

Example 6.



Example 6. N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2,3-cis)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide

To a solution of (2,3-cis)-3-amino-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride (103 mg), HOBt (58 mg), N-[(3,5-difluorophenyl)acetyl]-L-alanine (1e) (95 mg), and N-methyl morpholine (71 mg) in DMF (4 mL) was added EDAC-HCl (82 mg) . The mixture was stirred at RT under N_2 for 6h. The reaction mixture was diluted with water and extracted with ethyl acetate (3x). The organic extracts were combined, dried, filtered and evaporated. The crude product was purified by flash chromatography (1:1 Hexanes: ethyl acetate) to afford the title compound (75 mg) as an off-white solid. ^{1}H NMR (300 MHz, d6-DMSO) δ1.05 (d, 1.5H, J=7 Hz), 1.11 (d, 1.5H, J=7 Hz), 3.44 (m, 2H), 4.27 (m, 1H), 4.97 (m, 1H), 5.60 (t, 1H, J=6 Hz), 6.86-7.50 (m, 13H), 8.24 (d, 0.5H, J=7 Hz), 8.33 (d, 0.5H, J=7 Hz), 10.30 (d, 1H, J=7 Hz). MS APCI, m/z = 480 (M+H) LC/MS: 2.31 min.

The starting amine (2,3-cis)-3-amino-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride (6e) was prepared in the following manner:

a. Ethyl (2RS,3RS)-2-hydroxy-3-(2-nitrophenoxy)-3-phenylpropanoate (6a)
The title compound was prepared according to the published procedure of Carlo Banzatti, Franco Heidempergher, and Piero Melloni; J. Heterocyclic Chem. 20, 259 (1983).

b. Ethyl (2RS,3RS)-3-(2-aminophenoxy)-2-hydroxy-3-phenylpropanoate (6b)
To a solution of methyl (2RS,3RS)-2-hydroxy-3-(2-nitrophenoxy)-3-phenylpropanoate (3.995 g) in ethanol (150 mL) was added 5% palladium on carbon (500 mg) and the mixture was hydrogenated at 35 psi on a Parr shaker for 30 min. The reaction mixture was filtered through Celite and the resulting solution concentrated in-vacuo. The residue was purified by flash chromatography (ethyl acetate) to afford the title compound (3.740 g) as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ1.18 (t, 3H), 3.34 (m, 1H), 3.99 (br, 2H), 4.17 (m, 2H), 4.60 (m, 1H), 5.42 (d, 1H, J=3 Hz), 6.51-6.65 (m, 2H), 6.69-6.82 (m, 2H), 7.20-7.40 (m, 5H). MS APCI, m/z = 324 $(M+Na)^+$. LC/MS: 1.70 min.

c. (2,3-trans)-3-hydroxy-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (6c)
To a solution of methyl (2RS,3RS)-3-(2-aminophenoxy)-2-hydroxy-3-phenylpropanoate (3.585 g) in THF (100 mL) cooled to 0°C was added a solution of lithium hydroxide monohydrate (600 mg) in water (25 mL) and methanol (2 mL). After 15 min the cooling bath was removed and the mixture stirred an additional 45 min warming to ambient temperature. The reaction was re-cooled to 0°C and 1N aqueous hydrochloric acid (14.3 mL) was added. Solvent was then removed in-vacuo. The residue was dissolved in DMF (25 mL), HOBt (1.94 g), N-methyl morpholine (3.34 g), and EDAC (2.76 g) were added and the mixture stirred overnight under N_2 at ambient temperature. The reaction was diluted with water and extracted with ethyl acetate. The organic extracts were combined, dried , filtered and evaporated. The residue was purified by flash chromatography (2:1 Hexanes: ethyl acetate) to afford the title compound (1.05 g) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ3.70 (d,

1H, J=5 Hz), 4.63 (m, 1H), 5.28 (d, 1H, J=10 Hz), 6.89 (m, 1H), 7.02-7.16 (m, 3H), 7.35-7.47 (m, 5H), 7.78 (br, 1H). MS APCI, m/z = 256 (M+H). LC/MS: 1.84 min.

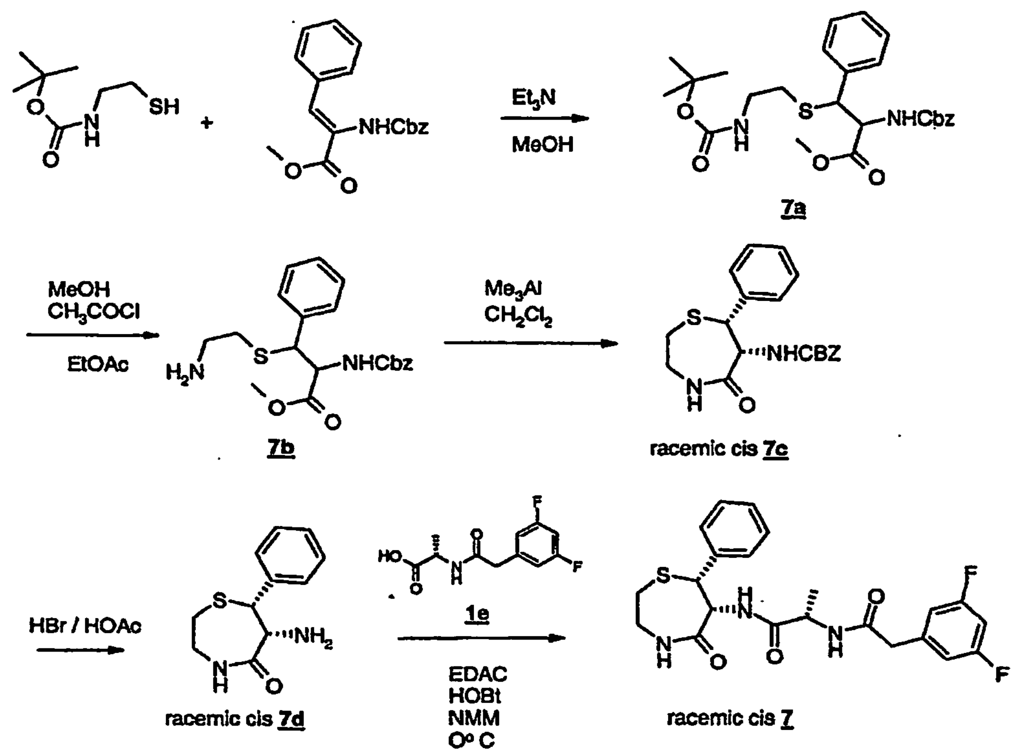
d. (2,3-cis)-3-azido-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (6d)

Trifluoromethanesulfonyl chloride (770 mg) was added via syringe to a solution of (2,3-trans)-3-hydroxy-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (765 mg) and triethylamine (508 mg) in dichloromethane (20 mL) under N_2 at 0°C. The mixture was kept at 0°C overnight. Additional trifluromethanesulfonyl chloride (770 mg) and triethylamine (508 mg) was added and the mixture kept at 0°C for an additional 4h. Additional trifluromethanesulfonyl chloride (1540 mg) and triethylamine (1016 mg) was added and the mixture kept at 0°C for an additional 3h. The reaction was concentrated *in vacuo* without heating, and the resulting residue immediately dissolved in DMF (5 mL) at 0°C under N_2. Sodium azide (650 mg) was added to the solution and the mixture allowed to warm to ambient temperature over 30 min. The reaction was diluted with water and extracted with ethyl acetate. The organic extracts were dried , filtered and evaporated. The residue was purified by flash chromatography (3:1 Hexanes: ethyl acetate) to afford the title compound (778 mg) as a foamy white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ4.45 (d, 1H, J=6Hz), 5.56 (d, 1H, J=6Hz), 7.00-7.07 (m, 1H), 7.10-7.26 (m, 3H), 7.40-7.46 (m, 3H), 7.51-7.61 (m, 3H). MS APCI, m/z = 253 ($M+H-N_2$). LC/MS: 2.25 min.

e. (2,3-cis)-3-amino-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride (6e)

To a solution of (2,3-cis)-3-azido-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (610 mg) in ethanol (40 mL) was added 5% palladium on carbon (65 mg) and 1N hydrochloric acid (2.4 mL). The mixture was stirred for 3h under 1 atmosphere of hydrogen. The mixture was filtered through Celite and the resulting solution was evaporated to afford the title compound (562 mg) as a tan solid. ^{1}H NMR (300 MHz, d6-DMSO) δ4.55 (d, 1H, J=7 Hz), 5.85 (d, 1H, J=7 Hz), 7.06-7.62 (m, 9H), 8.29 (br, 3H), 10.64 (s, 1H). MS APCI, m/z = 255 (M+H). LC/MS: 1.29 min.

Example 7



Example 7. (2*S*)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(*6RS,7RS*)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]propanamide (7)

Using a procedure similar to that described in Example 1, except using (6,7-*cis*)-6-amino-7-phenyl-1,4-thiazepan-5-one (7d)(84.3 mg) as the amine component and isolation of title compound by Et_2O trituration of the crude material, the title compound (7) was obtained as a white solid (99.8 mg, 59%), m.p. 128-133°. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, 1.5H), 1.28 (d, 1.5H), 2.80 (m, 1H), 3.06 (m, 1H), 3.49 (d, 2H), 3.76 (m, 2H), 4.32 (m, 1H), 4.47 (m, 1H), 5.25 (t, 0.5H), 5.33 (t, 0.5H), 6.09 (d, 0.5 , exchangeable) 6.25 (m, 1H, exchangeable), 6.38 (t, 0.5H, exchangeable), 6.79 (m, 3H), 7.00 (d, 0.5H, exchangeable), 7.08 (d, 0.5H, exchangeable) 7.24 (m , 5H). MS APCI, m/z = 448(M^+). HPLC Method A: 2.62 min.

The starting amine (6,7-*cis*)-6-amino-7-phenyl-1,4-thiazepan-5-one (7d) was prepared in the following manner:

b. **Methyl 2-{[(benzyloxy)carbonyl]amino}-3-({2-[(*tert*-butoxycarbonyl)amino]ethyl}thio)-3-phenylpropanoate (7a)**

Using a method similar to that described in Example 1, part b (Method B) a solution of tert-butyl N-(2-mercaptoethyl)carbamate (2.4 mL), methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-phenylprop-2-enoate (0.87 g), triethylamine (0.39 mL) and methanol (15 mL) was stirred at RT for 3 days. Removal of the solvent and chromatograpy of the resultant crude oil on silica gel (10% to 25% ethyl acetate / hexanes) returned the title compound as a viscous oil (1.22 g, 90%). The proton NMR displayed a mixture of diastereomers of approximate ratio 7:3; the major diastereomer is reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.48 (t, 2H), 3.19 (br, 2H), 3.65 (s, 3H), 4.12 (q, 1H), 4.35 (t, 1H), 4.73 (t, 2H), 5.09 (d, 2H), 7.27-7.34 (m, 10H). MS APCI, m/z = 389(M - t-BuOCO)$^+$. HPLC Method A: 3.47 min.

b. **Methyl 3-[(2-aminoethyl)thio]-2-{[(benzyloxy)carbonyl]amino}-3-phenylpropanoate (7b)**

To a stirred cooled (ice-bath) solution of methyl 2-{[(benzyloxy)carbonyl]amino}-3-({2-[(*tert*-butoxycarbonyl)amino]ethyl}thio)-3-phenylpropanoate (7a) (1.20 g) and methanol (0.284 mL) in ethyl acetate (2 mL) was added dropwise from a syringe acetyl chloride (0.43 mL) and the mixture stirred in the ice bath for an additional 10 min and then at RT for 50 min. Excess Et_2O was added and the white solid collected, dissolved in water, treated with an excess of sat. aqueous K_2CO_3 and extracted once with CH_2Cl_2 and twice with Et_2O. The dried organics ($MgSO_4$) were filtered and the solvent removed to yield the title compound as an oil (0.86 g, 90%). The proton NMR displayed a mixture of diastereomers of approximate ratio 7:3; the major diastereomer is reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ1.46 (s, 2H, exchangeable), 2.47 (t, 2H), 2.76 (t, 2H), 3.66 (s, 3H), 3.35 (d, 1H), 4.75 (t, 1H), 5.09 (m, 2H), 5.76 (d, 1H, exchangeable), 7.28-7.34 (m, 10H). MS APCI, m/z = 389(M$^+$). HPLC Method A: 2.27 min.

c. **Benzyl (6,7 *cis*)-5-oxo-7-phenyl-1,4-thiazepan-6-ylcarbamate (7c)**

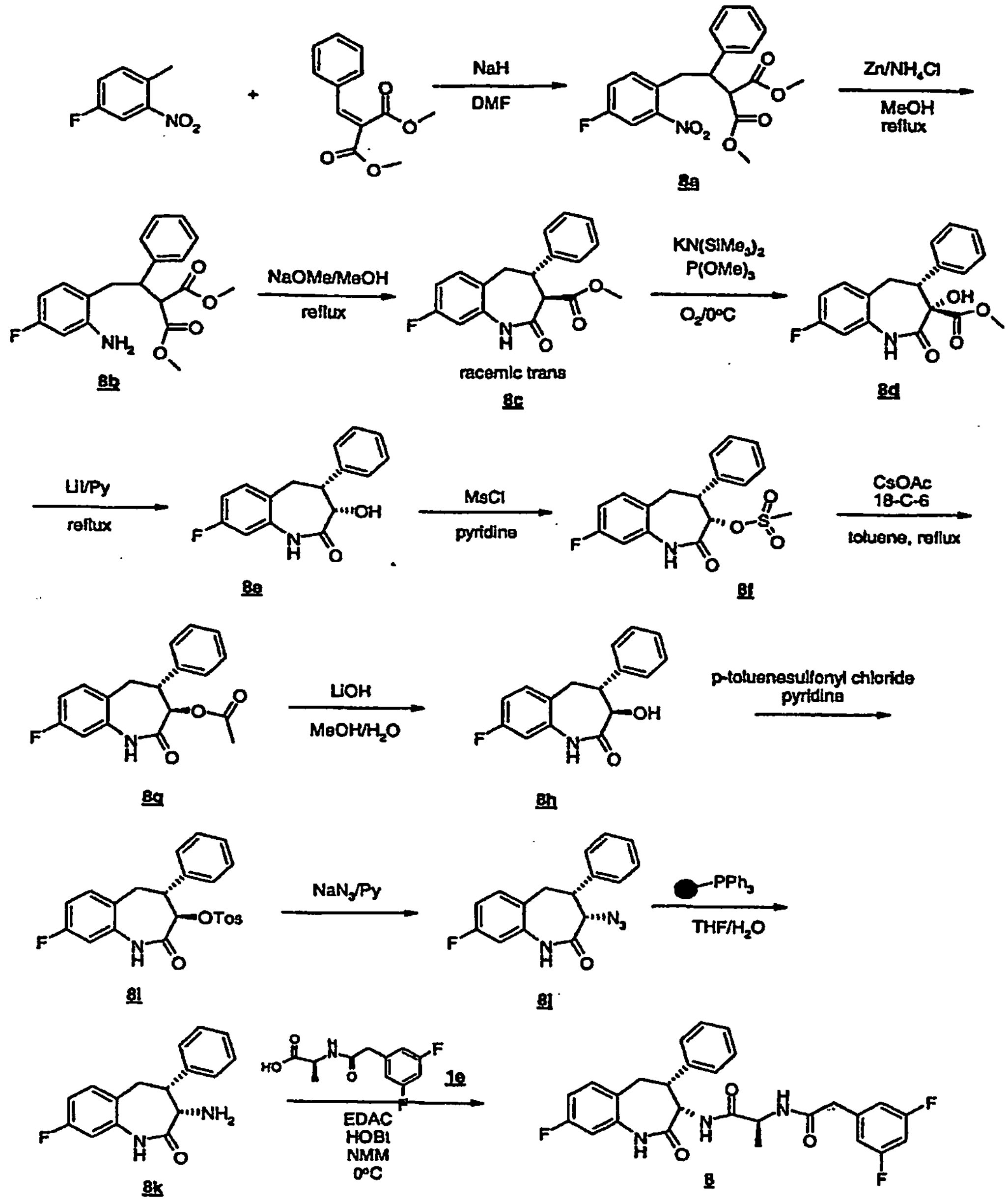
To a stirred solution of methyl 3-[(2-aminoethyl)thio]-2-{[(benzyloxy)carbonyl]amino}-3-phenylpropanoate (7b) (0.85 g) in CH_2Cl_2 (10 mL) was added 2.0 M $(CH_3)_3Al$ in toluene (2.2 mL) and the mixture stirred overnight at

RT. The reaction mixture was cautious treated with 0.5N hydrochloric acid (20 mL total) and extracted twice with CH_2Cl_2. The dried extracts ($MgSO_4$) yielded the title compound as a mixture with the 6,7-*trans* diastereomer; HPLC Method A: 2.96 and 3.22 min.. Trituration with Et_2O returned pure title compound as a white solid (0.32 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ2.75-2.81 (m, 1H), 3.02-3.08 (m, 1H), 3.68-3.93 (M, 2H), 4.35 (d, 1H, $J_{6,7}$=3.8 Hz), 5.11 (2H), 5.23 (q, 1H, $J_{6,7}$=3.8 Hz), 6.02 (d, 1H, NH), 6.13 (br s, 1H, NH) 7.26-7.38 (m, 10H). MS APCI, m/z = 357(M^+). HPLC Method A: 2.96 min.

d. **(6,7 *cis*)-6-Amino-7-phenyl-1,4-thiazepan-5-one (7d)**

To benzyl (6,7 *cis*)-5-oxo-7-phenyl-1,4-thiazepan-6-ylcarbamate (7c) (0.30 g) was added 30% HBr / HOAc (3 mL) and magnetic stirring initiated. After a few minutes the evolution of CO_2 was evident. After 45 min. the mixture was treated with excess Et_2O and the white solid collected by filtration, dissolved in water (~65 mL), treated with excess saturated aqueous sodium bicarbonate and extracted 10 times with CH_2Cl_2 (25 mL portions). The dried CH_2Cl_2 extracts ($MgSO_4$) yielded the title compound as a white solid (0.17 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ1.70 (br s, 2H, NH_2), 2.75-2.82 (m, 1H), 2.95-3.02 (m, 1H), 3.68-3.87 (m, 2H), 4.14 (d, 1H, $J_{6,7}$=3.1 Hz), 4.33 (d, 1H, $J_{6,7}$=3.1 Hz), 6.13 (br s, 1H, NH), 7.29-7.42 (m, 5H). MS APCI, m/z = 223(M^+). HPLC Method A: 0.63 min.

Example 8


NaH
DMF
Zn/NH$_4$Cl
MeOH
reflux
8a
8b
NaOMe/MeOH
reflux
racemic trans
8c
KN(SiMe$_3$)$_2$
P(OMe)$_3$
O$_2$/0°C
8d
LiI/Py
reflux
8e
MsCl
pyridine
8f
CsOAc
18-C-6
toluene, reflux
8g
LiOH
MeOH/H$_2$O
8h
p-toluenesulfonyl chloride
pyridine
OTos
8i
NaN$_3$/Py
8j
PPh$_3$
THF/H$_2$O
8k
1e
EDAC
HOBt
NMM
0°C
8

Example 8. N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3,4-*cis*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide

To a solution of (3,4-*cis*)-3-amino-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8k) (15 mg) in dichloromethane (6 mL) at 0°C under N_2 was added N-[3,5-difluorophenyl)acetyl]-L-alanine (8e) (14 mg), HOBT-hydrate (15 mg), EDAC-HCl (16 mg) and N-methyl morpholine (14 μL). The reaction mixture was stirred for 1h at 0°C and then for 2h at RT. The mixture was concentrated in vacuo and then partitioned between water (10mL) and ethyl acetate(12mL). The organic phase was collected and consecutively washed with water, saturated aqueous sodium bicarbonate, and brine, dried , filtered and evaporated to yield the title compound (14 mg, 52%) as off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 0.86 (d 1.5H), 0.97 (d, 1.5H), 2.8 (m, 2H), 3.76 (s, 2H), 3.86 (m, 1H), 4.02 (m, 1H), 4.53 (t, 1H), 6.68-6.78 (m, 3H), 6.99 (m, 2H), 7.17-7.39 (m, 5H). LC/MS: m/z = 496 (M^+ + H), 518 (M^+ + Na), retention time = 2.41 min.

The starting amine, (3,4-*cis*)-3-amino-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8k), was prepared in the following manner:

a. Dimethyl [2-(4-fluoro-2-nitrophenyl)-1-phenylethyl]malonate (8a).

A solution of benzylidene malonate (14.2g) in DMF (280mL) was treated with sodium hydride (2.57g, 95%). A solution of 4-fluoro-2-nitrotoluene in DMF (10 mL) was added over 1 H, and the reaction mixture was stirred at RT overnight and then quenched by the addition of glacial acetic acid (175 mL) at 0°C. A total of 500 mL of 70:30 water-methanol was added with stirring, and the organics were extracted with ethyl acetate. The organic extracts were combined and washed with saturated aqueous potassium carbonate solution (2 ×) and brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give a dark brown oil. Flash chromatography on silica gel (75:25 hexane-ethyl acetate, then 50:50 hexane-ethyl acetate) provided 7.0 g (30 %) of the title compound as a red-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (d, 2H), 3.73 (d, 1H), 4.32 (m, 1H), 7.09-7.29 (m, 7H), 7.71 (m, 1H). LC/MS: m/z = 398 $(M + Na)^+$, retention time = 2.66 min.

b. Dimethyl [2-(2-amino-4-fluorophenyl)-1-phenylethyl]malonate (8b).

To a solution of dimethyl [2-(4-fluoro-2-nitrophenyl)-1-phenylethyl] malonate (**8a**) (5.0 g) in methanol (20 mL) was added ammonium chloride (1.5 g) and zinc dust (11.0 g). The reaction mixture was then heated to reflux for 1h. The reaction mixture was filtered through a Celite pad, and the organic solvents were removed in vacuo. The resulting yellow oil was dissolved in ethyl acetate (100 mL) and washed with saturated aqueous potassium carbonate solution (2 ×), the organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to afford the title compound as a tan gum (4.1 g, 90 %). LC/MS: m/z = 346 $(M + H)^+$, retention time = 2.51 min.

c. Methyl (3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine-3-carboxylate (8c).

A solution of dimethyl [2-(2-amino-4-fluorophenyl)-1-phenylethyl] malonate (**8b**) (4.3 g) in methanol (130 mL) was treated with sodium methoxide (1.73 g). The reaction mixture was heated to reflux for 5h, cooled to room temperature, and acidified with 1N hydrochloric acid. The methanol was evaporated in vacuo, the residue was extracted with ethyl acetate, and the extract was washed with brine, 1N hydrochloric acid, and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting crude product (4.0 g) was triturated with 1:1 diethyl ether:ethyl acetate to give the title compound as a colorless solid (3.87 g, 93 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (m, 2H), 3.23 (m, 1H), 3.72 (s, 3H), 3.77 (m, 1H), 6.71-7.50 (m, 7H), 8.95 (s, 1H). LC/MS: m/z = 336 $(M + Na)^+$, retention time = 2.28 min.

d. Methyl (3,4-*cis*)-8-fluoro-3-hydroxyl-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine-3-carboxylate (8d).

A solution of methyl (3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine-3-carboxylate (8c) (156 mg) in THF (10 mL) was cooled to –78 °C under nitrogen. Potassium hexamethyldisilazide (0.5 M in toluene, 4.0 mL, 4 equiv) was added, and the reaction mixture was stirred for 1h at –78 °C. Trimethyl phosphite (0.24 mL, 4 equiv) was added, and bubbling with oxygen gas through the solution was started. Bubbling with oxygen gas was continued while the temperature was allowed to warm to 0°C over approximately 30 min. The reaction was quenched with acetic acid (7 mL), the solvents were partially removed in vacuo, ethyl acetate was added, and the organic layer was washed with 1N hydrochloric acid (2 ×), saturated

potassium carbonate (2 ×), and brine, dried over sodium sulfate, filtered, and concentrated in vacuo to provide the title compound as a light yellow solid (130 mg, 80 %). LC/MS: m/z = 330 $(M + H)^+$, retention time = 2.22 min.

e. (3,4-*cis*)-8-Fluoro-3-hydroxyl-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8e).

A solution of methyl (3,4-*trans*)-8-fluoro-3-hydroxyl-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine-3-carboxylate (8d) (1.4 g) and LiI (2.3 g, 4 equiv) in pyridine (35 ml) and water (0.35 mL) was heated to reflux for 3h. Pyridine was removed in vacuo, ethyl acetate was added, and the ethyl acetate solution was washed with 1N hydrochloric acid (3 ×), saturated aqueous potassium carbonate solution, and brine, dried over sodium sulfate, and filtered. A small amount of insoluble material was collected from the separatory funnel. This material was washed several times with water and ether, and then used to seed the ethyl acetate solution. Refrigeration and filtration provided the title compound as an off-white solid (700 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78-2.05 (m, 2H), 2.87 (m, 1H), 4.20 (m, 1H), 4.43 (d, 1H), 6.71-7.75 (m, 7H), 8.35 (s, 1H). LC/MS: m/z = 272 $(M + H)^+$, retention time = 1.95 min.

f. (3,4-*cis*)-8-Fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl methanesulfonate (8f).

To a solution of (3,4-*cis*)-8-fluoro-3-hydroxyl-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8e) (400 mg) in pyridine (3 mL) was added methylsulfonyl chloride (0.17 mL, 1.5 equiv) at 0°C. The reaction mixture was stirred for 3h at 0°C, and then diluted with diethyl ether (50 mL), washed several times with water, 1N hydrochloric acid (3 ×), saturated aqueous sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford the title compound as a white solid (512 mg, 90.9%). LC/MS: m/z = 350 $(M + H)^+$, retention = 2.58 min.

g. (3,4-*trans*)-8-Fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl acetate (8g).

To a solution of (3,4-*cis*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl methanesulfonate (<u>8f</u>) (512 mg) in toluene (10 mL) was added 18-crown-6 (391.2 mg) and cesium acetate (2.8 g) at RT under N_2. The reaction mixture was refluxed overnight and then washed consecutively with water (several times), brine, 1N hydrochloric acid (2 ×), saturated aqueous sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford light yellow solid (394 mg, 85 %) as trans racemic. LC/MS: m/z = 314 $(M + H)^+$, retention time = 2.56 min.

<u>h. (3,4-*trans*)-8-Fluoro-3-hydroxy-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8h).</u>

To a solution of (3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl acetate (<u>8g</u>) (360 mg) in methanol (10 mL) with water (5 mL) was added lithium hydroxide (46 mg, 2 equiv). The reaction mixture was stirred at RT for 5h, and it was then acidified to pH = 1 with 1N hydrochloric acid. The mixture was extracted with ethyl acetate twice and the combined ethyl acetate layers were washed with water, and brine, dried over sodium sulfate, filtered and concentrated in vacuo. Flash chromatography (hexane: ethyl acetate = 4:1) provided the title compound (218.20 mg, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8-2.15 (m, 2H), 2.9 (m, 1H), 4.30 (m, 1H), 4.53 (d, 1H), 6.71-7.5 (m, 7H), 7.95 (s, 1H).
LC/MS: m/z = 272 $(M + H)^+$, retention time = 1.94 min.

<u>i. (3,4-*trans*)-8-Fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl 4-methylbenzensulfonate (8i).</u>

To a solution of (3,4-*trans*)-8-fluoro-3-hydroxy-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (<u>8h</u>) (140.0 mg) in pyridine (4 mL) was added p-toluenesulfonyl chloride (170.0 mg, 2.3 equiv) at 0°C. The reaction mixture was stirred for 3h at 0°C, and then for 24h at RT. The reaction mixture was then diluted with dichloromethane (50 mL), and washed several times with water, saturated aqueous copper sulfate, and brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford the title compound as a brown oil (153.7 mg, 70 %). LC/MS: m/z = 426 $(M + H)^+$, retention = 2.74 min.

j. (3,4-*cis*)-3-Azido-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8j).

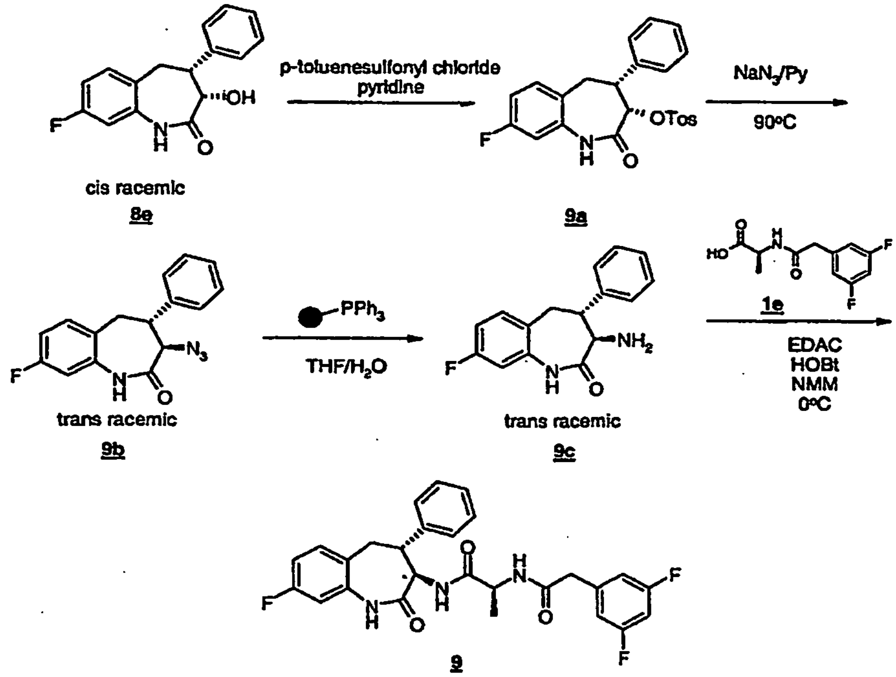
To a solution of (3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl 4-methylbenzensulfonate (8i) (220.0 mg) in DMF (4 mL) was added sodium azide (135.2 mg, 4.0 equiv) at RT. The reaction mixture was heated to 90 ^{0}C for 24h, cooled to RT, diluted with ethyl acetate (50 mL), and washed several times with water and brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide a brown residue. Flash chromatography (hexane: ethyl acetate = 4:1) provided the title compound (87.0 mg, 58.7 %). LC/MS: m/z = 297 $(M + H)^+$, retention time = 2.46 min.

k. (3,4-*cis*)-3-Amino-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8k).

To a solution of (3,4-*cis*)-3-azide-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8j) (65.0 mg) in THF (5 mL) was added PS-triphenylphosphine (1.0 g, 1.2 mmol/g, 5.5 equiv) at RT. The reaction mixture was stirred at RT for 24h. The mixture was filtered, and the resin was extracted with THF (10 mL × 2) and ethyl acetate (10 mL). The combined organic extracts were concentrated in vacuo to provide a brown residue. Flash chromatography (hexane: ethyl acetate = 1:1) provided the title compound (45.7 mg, 70.0 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.52 (m, 2H), 1.98 (s, 2H), 2.94 (m, 1H), 3.85 (d, 1H), 6.62-7.74 (m, 8H). ^{19}F NMR (300 MHz, $CDCl_3$) δ -113.0.

LC/MS: m/z = 271 $(M + H)^+$, retention time = 1.44 min.

Example 9.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pyridine
OTos
NaN_3/Py
90°C
cis racemic
8e
9a
N_3
PPh3
THF/H_2O
NH_2
1e
EDAC
HOBt
NMM
0°C
trans racemic
9b
trans racemic
9c
9

Example 9. N^2-[(3,5-Difluorophenyl)acetyl]-N^1-[(3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-terahydro-1H-1-benzazepin-3-yl]-L-alaninamide

To a solution of (3,4-*trans*)-3-amino-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9c) (30 mg) in dichloromethane (12 mL) at 0°C under N_2 was added N-[3,5-difluorophenyl)acetyl]-L-alanine (1e) (28 mg), HOBT-hydrate (30 mg), EDAC-HCl (32 mg) and N-methyl morpholine (28 μL). The reaction mixture was stirred for 1h at 0°C and then for 2h at RT. The mixture was concentrated in vacuo and consecutively washed with water, saturated aqueous sodium bicarbonate, and brine, dried over sodium sulfate, filtered and evaporated to yield the title compound (30 mg, 54%) as an off-white solid. NMR studies revealed a mixture of 2 trans diastereomers. ^{1}H NMR (400 MHz, CD_3OD) δ 0.60 (d 1.5H), 1.12 (d, 1.5H), 2.6 (d, 1H), 3.23 (d, 1H), 3.56 (m, 1H), 4.16 (t, 1H), 4.58 (m, 1H), 6.88-7.44 (m, 8H), 8.0 (d, 1H), 8.1 (d, 1H), 8.2 (d, 1H), 9.90 (d, 1H). LC/MS: m/z = 496, (M^+ + H) and 518 $(M + Na)^+$, retention time = 2.35 min.

The starting amine, (3,4-*trans*)-3-amino-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9c), was prepared in the following manner:

a. (3,4-*cis*)-8-Fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl 4-methylbenzensulfonate (9a).

To a solution of (3,4-*cis*)-8-fluoro-3-hydroxyl-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (8e) (140.0 mg) in pyridine (4 mL) was added p-toluenesulfonyl chloride (170.0 mg, 2.3 equiv) at 0°C. The reaction mixture was stirred for 3h at 0°C, then for 24h at RT. It was then diluted with dichloromethane (50 mL), and washed several times with water, saturated aqueous copper sulfate, and brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford the title compound as a brown oil (140.0 mg, 63.6 %). LC/MS: m/z = 426 $(M + H)^+$, retention time = 2.72 min.

b. (3,4-*trans*)-3-Azido-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9b).

To a solution of (3,4-*cis*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl 4-methylbenzensulfonate (9a) (220.0 mg) in DMF (4 mL) was added sodium azide (135.2 mg, 4.0 equiv) at RT. The reaction mixture was heated to 90°C

for 24h, cooled, diluted with ethyl acetate (50 mL), and washed several times with water and brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide a brown residue. Flash chromatography (hexane: ethyl acetate = 4:1) afforded the title compound (70.0 mg, 47.2 %). LC/MS: m/z = 297 $(M + H)^+$, retention time = 2.44 min.

c. (3,4-*trans*)-3-Amino-8-fluoro--4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9c).

To a solution of (3,4-*trans*)-3-azide-8-fluoro-4-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9b) (65.0 mg) in THF (5 mL) was added PS-triphenylphosphine (1.0 g, 1.2 mmol/g, 5.5 equiv) at RT. The reaction mixture was stirred at RT for 24h. The mixture was filtered, and the resin was extracted with THF (10 mL × 2) and ethyl acetate (10 mL). The combined organic extracts were concentrated in vacuo to provide brown residue. Flash chromatography (hexane: ethyl acetate = 1:1) provided the title compound (40.0 mg, 60.0 %). ^1H NMR (300 MHz, $CDCl_3$) δ 1.42-1.52 (m, 2H), 1.98 (s, 2H), 2.94 (m, 1H), 3.85 (d, 1H), 6.62-7.74 (m, 8H). LC/MS: m/z = 272 $(M + H)^+$. NMR studies revealed a mixture of 2 trans diastereomers.

Utility

The compounds of the present invention have utility for the prevention and treatment of Alzheimer's disease by inhibiting amyloid β production. Methods of treatment target formation of amyloid β production through enzymes involved in the proteolytic processing of β amyloid precursor protein. Compounds that inhibit β and γ secretase activity, either directly or indirectly, controls the production of amyloid β. The inhibitions of β and γ secretases reduce the production of amyloid β and are thought to reduce or prevent the neurological disorders such as Alzheimer's disease. The compounds of the present invention have utility for the prevention and treatment of disorders involving amyloid β production, such as cerebrovascular disorders.

Compounds of the present invention have been shown to inhibit amyloid β production, as determined by the gamma secretase detergent extract assay and gamma secretase whole cell described below.

Compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit amyloid β production. These would be provided in commercial kits comprising a compound of this invention.

As used herein "ug " denotes microgram, "mg" denotes milligram, "g" denotes gram, "uL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, ".uM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar, "nm" denotes nanometer, "DMSO" denotes dimethyl sulfoxide, "DTT" denotes, "DPBS" denotes "EDTA" denotės ethylenediaminetetraacetate,

Gamma Secretase Detergent Extract Assay

The gamma secretase enzyme assay measures the amount of amyloid β (Aβ)40 product generated by the cleavage of C100, a truncated form of amyloid precursor protein (APP). The C100 substrate is a recombinant protein purified from *E. coli* inclusion bodies. The γsecretase enzyme complex is prepared by detergent extraction of HeLa 8A8 cell membranes. The enzyme reaction contains 10μl of inhibitor at a defined concentration, diluted from a DMSO stock into 96-well microplates (final concentration of DMSO is maintained at 5%). 20ul of the C100 substrate (600 nM final concentration), in reaction buffer, (50 mM MES, pH 6.5, containing 100mM NaCl, 1 mM EDTA, 1 mM DTT, 1 mg/mL BSA, 0.25% Chapso, 0.01% PE, 0.01% PC and a protease cocktail), is added to the plates. The reactions are initiated by addition of 10ul enzyme at a 20-fold dilution from stock. An Aβ40 standard curve diluted in the reaction buffer plus C100 is included in each assay. Plates are incubated for 3 hours at 37 degrees. After the incubation period, 50μl of an antibody mixture is added: rabbit anti-Aβ40 antibody (Biosource #44-3481) at 0.16 ug/ml and biotinylated 4G8 (Senetek #240-10) at 0.25 ug/ml in DPBS (Fisher # MT21031CV) containing 0.5% bovine serum albumin, 0.5% Tween 20. Plates are then incubated overnight at 4 degrees. The following morning, a 50ul mixture of 0.0625 mg/ml

Ruthenium labeled goat anti-rabbit IgG (labeled in-house) and 125 ug/ml of Streptavadin beads (Igen #M280), diluted in the same DPBS buffer, is added to detect the cleaved product. After a one hour incubation period at room temperature, an Igen M Series instrument is utilized to quantitate the results by electrochemiluminescence.

Gamma Secretase Whole Cell assay (GSWC)

Preparation of cells for assay

Human Embryonic Kidney (HEK) cells stably expressing human Amyloid Precursor protein (APP) and Presenelin I were grown in DMEM media (Fisher MT10013CV) containing 10% fetal calf serum (Fisher #MT135011CV), 0.2 mg/mL G418 (Fisher #MT30234CR) and 1X concentration of antibiotic/antimycotic mixture (Fisher #MT30004CI). Cells were grown in tissue culture flasks and passaged every week at a ratio of 1:30.

Thirty minutes prior to incubation with test compounds, cells were harvested by treating the monolayer with DPBS (Fisher #MT21031CV) containing 3 mM EDTA. Cells were resuspended at a density of 2 million cells/mL in complete growth medium.

Aβ 40 assay

Test compounds were solubilized in DMSO at a concentration of 3.3 mM. From this stock solution a dilution series was prepared in complete growth medium of cells. Dilution series were then transferred to 96 well assay plate (Costar #3595) with 100 μL in each well. Cells (100 μL) were added to each well containing test compound. Two controls, one containing only cells (Total) and one containing only growth medium (Background) were also included. Cells were incubated with compounds for 14-16 hours in cell culture incubator.

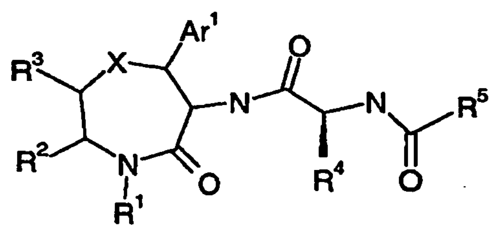
At the end of 14-16 hour incubation, 100 μL of supernatant was transferred from each well in to a polypropylene 96 well plate. This supernatant was mixed with 100 μL of DPBS (Fisher # MT21031CV) containing 0.5% bovine serum albumin, 0.5% Tween 20, 0.25 μg/mL of biotinylated 4G8 (Senetek #240-10), 0.18 μg/mL rabbit anti-Aβ40

antibody (Biosource #44-3481), 0.045 μg/mL Ruthenium labeled goat anti-rabbit IgG (labeled in-house) and 60 μg/mL of Streptavadin beads (Igen #M280). The mixture was incubated for 4-6 hours at 4°C on a plate shaker.

At the completion of 4-6 hour incubation, plate was brought to room temperature and the generated Aβ40 was detected using the Igen M8 analyzer. Raw data was imported into Microsoft Excel software. IC_{50} values for inhibition of Aβ40 generation by test compounds were calculated using Excel-Fit.

Claims:

1. A compound of structural diagram (I):



wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 2 sulfur atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, 2 or 3 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5 or 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, or substituted phenyl with 0, 1, 2, or 3 R^e;

R^d is, at each occurrence independently selected from C_{1-3}alkyl, C_{1-3}alkoxy, or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl, aryl, or heteroaryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is $C_{1-3}alkylR^9$ or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, $C_{1-4}alkyl$, OH, SH, CH_2SCH_3, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, $C_{1-4}alkylamine$, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, 2 or 3 R^e;

R^{10} is alkyl or R^9;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}alkenyl$, $C_{2-4}alkylNR^aR^b$, $C_{1-4}alkylCOR^d$; or $C_{1-3}alkylphenyl$ substituted with 0, 1, or 2 R^c;

R^a and R^b are, at each occurrence independently selected from H, $C_{1-4}alkyl$ or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, $C_{1-3}alkyl$, or phenyl;

R^d is, at each occurrence independently selected from $C_{1-3}alkyl$, or NR^aR^b;

R^e is, at each occurrence independently selected from OH, F, Cl, Br, I, CN, NO_2, CF_3, $C_{1-3}alkyl$, or $C_{1-3}alkoxy$;

R^2 and R^3 are at each occurrence independently selected from H, $C_{1-6}alkyl$, C_{4-6} cycloalkyl, or aryl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is NO_2, F, Cl, Br, I, CF_3, CN, C_1-3alkyl, or C_1-3alkoxy;

R^4 is H or CHR^7R^8;

R^5 is $C_{1-3}alkylR^9$ or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, $C_{1-4}alkyl$, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, $C_{1-4}alkylamine$, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 0, 1, or 2 R^e;

R^{10} is alkyl or R^9;

3. A compound of claim 1,

wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 2 oxygen atoms or 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, 1, or 2 R^e;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 5-membered N-linked heterocycle having 2 nitrogen or, 1 nitrogen and 1 oxygen, ring atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl, phenyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl or NR^aR^b;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, C_{4-6} cycloalkyl or aryl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, NO_2, F, Cl, Br, I, CF_3, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, indole, imidazole, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

4. A compound of claim 1,

wherein:

X is C, O, NR^1, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, 2, or 3 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms, but no more than 1 oxygen and 1 sulfur atom;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d; or C_{1-3}alkylphenyl substituted with 0, or 1 R^c;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle having 2 nitrogen atoms, wherein the non-linked nitrogen is substituted with R^c;

R^c is, at each occurrence independently selected from H, C_{1-3}alkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CN, NO_2, CF_3, C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from H, C_{1-6}alkyl, or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3, C_{1-6}alkyl;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

n is 0, 1 or 2;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, CH_2CO_2H, $(CH_2)_3NHCH(NH_2)_2$, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

5. A compound of claim 1, wherein:

X is C, O, SO_2 or S;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring optionally substituted with 0, 1, or 2 R^e moieties, said ring having 0, 1, or 2 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl, or R^a and R^b and the N to which they are attached in combination form a 6-membered N-linked heterocycle;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, NO_2, CF_3, or C_{1-6}alkyl;

R^2 and R^3 are at each occurrence independently selected from C_{1-6}alkyl or R^2 and R^3 in combination form a fused phenyl moiety that may be substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, C_{1-4}alkyl, OH, $CONH_2$, CH_2CONH_2, CO_2H, C_{1-4}alkylamine, phenyl or hydroxyphenyl;

R^9 is phenyl substituted with 1, or 2 R^e;

R^{10} is alkyl or R^9;

6. A compound of claim 1, wherein:

X is C, O, SO_2 or S;

Ar^1 is a 6-membered aromatic or heteroaromatic ring having 0, or 1 nitrogen, oxygen or sulfur atoms;

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkylNR^aR^b, C_{1-4}alkylCOR^d;

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl or C_{5-6}cycloalkyl;

R^d is, at each occurrence independently selected from C_{1-3}alkyl;

R^e is, at each occurrence independently selected from H, OH, F, Cl, Br, I, CF_3;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f moieties,

R^f is H, F, Cl, Br, I, or CF_3;

R^4 is H or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$;

R^7 and R^8 are, at each occurrence independently selected from H, or OH;

R^9 is phenyl substituted with 2 R^e;

R^{10} is R^9;

7. A compound of claim 1, wherein X is C, O, SO_2 or S.

8. A compound of claim 1, wherein:

Ar^1 is a 5-or 6-membered aromatic or heteroaromatic ring optionally substituted with 0 or 1 R^e said ring having 1 nitrogen, oxygen or sulfur atom.

9. A compound of claim 1, wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b.

10. A compound of claim 1, wherein:

R^a and R^b are, at each occurrence independently selected from H, C_{1-4}alkyl.

11. A compound of claim 1, wherein:

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0, 1 or 2 R^f.

12. A compound of claim 1, wherein:

R^e is, at each occurrence independently selected from F or Cl.

13. A compound of claim 1, wherein R^f is F or Cl.

14. A compound of claim 1, wherein R^4 is H or CHR^7R^8.

15. A compound of claim 1, wherein R^5 is C_{1-3}alkylR^9 or $CH(OH)R^{10}$.

16. A compound of claim 1, wherein:

R^7 and R^8 are, at each occurrence independently selected from H or OH.

17. A compound of claim 1, wherein R^9 is phenyl substituted with 2 R^e.

18. A compound of claim 1, wherein R^{10} is phenyl substituted with 2 R^e.

19. A compound of claim 1, wherein:

X is C, O, SO_2 or S;

R^1 is H, C_{1-6}alkyl, C_{3-6} cycloalkyl, C_{2-4}alkylNR^aR^b;

R^a and R^b are, at each occurrence independently selected from H,or C_{1-4}alkyl;

R^2 and R^3 are combined to form a fused phenyl moiety substituted with 0,1 or 2 R^f;

R^e is, at each occurrence F;

R^f is F or Cl;

R^4 is H, or CHR^7R^8;

R^5 is C_{1-3}alkylR^9 or CH(OH)R^{10};

R^7 and R^8 are, at each occurrence independently selected from H or OH;

R^9 is phenyl 3, 5-disubstituted with F;

R^{10} is phenyl 3, 5-disubstituted with F.

20. A compound of formula (I) selected from:
(2S)-N-[(2S,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2S)-N-[(2R,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2S)-N-[(2S,3R)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2S)-N-[(2R,3S)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;
(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;
(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;
(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]propanamide;
(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;
(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3S)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2S,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3S)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3S)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2S,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2R,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(3,4-dichlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-2-(4-chlorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]-L-alaninamide;

N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-(phenylacetyl)-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(4-methylphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2S,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2R,3S)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^1-[(2S,3R)-7-chloro-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3R,4S)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3S,4R)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(2-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-4-oxo-2-(3-thienyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(2-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-2-(3-furyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2R,3R)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(2S)-2-hydroxy-4-methylpentanoyl]-N^1-[(2S,3S)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2S,3S)-5-methyl-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;
N^1-[(2S,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;
N^1-[(2R,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;
N^1-[(2R,3S)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;
N^1-[(2S,3R)-7-chloro-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6R,7S)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;
N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(6S,7R)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]-L-alaninamide;
(2*S*)-*N*-[(2*S*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2*S*)-*N*-[(2*R*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2*S*)-*N*-[(2*S*,3*R*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2*S*)-*N*-[(2*R*,3*S*)-7-chloro-2-(2,5-difluorophenyl)-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;
(2*S*)-*N*-[(2*S*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*S*,3*R*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

(2*S*)-*N*-[(2*R*,3*S*)-2-(3-chlorophenyl)-5-methyl-1,1-dioxido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-2-{[(3,5-difluorophenyl)acetyl]amino}propanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2*R*,3*R*)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^1-[(2,3-*cis*)-5-cyclohexyl-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-N^2-[(3,5-difluorophenyl)acetyl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-{(2R,3R)-2-(2,5-difluorophenyl)-5-[2-(dimethylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl}-L-alaninamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(2R,3R)-2-(2,5-difluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-3-hydroxypropanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2R,3R)-2-(2,5-difluorophenyl)-5-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl]-L-alaninamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(2,3-cis)-4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-yl]-L-alaninamide;

(2S)-2-{[(3,5-difluorophenyl)acetyl]amino}-N-[(*6RS,7RS*)-5-oxo-7-phenyl-1,4-thiazepan-6-yl]propanamide;

N^2-[(3,5-difluorophenyl)acetyl]-N^1-[(3,4-*cis*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-3-yl]-L-alaninamide;

N^2-[(3,5-Difluorophenyl)acetyl]-N^1-[(3,4-*trans*)-8-fluoro-2-oxo-4-phenyl-2,3,4,5-terahydro-1H-1-benzazepin-3-yl]-L-alaninamide

or a pharmaceutical acceptable salt thereof.

21. A compound according to any one of claims 1 to 21, for use as a medicament.

22. The use of a compound as defined in any one of claims 1 to 21, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with β-amyloid production, Alzheimer's disease, or Down's Syndrome.

23. A method for the treatment of neurological disorders associated with β-amyloid production comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of claim 1.

24. A method for inhibiting γ-secretase activity comprising administering to a host in need of such inhibition a therapeutically effective amount of a compound of claim 1 that inhibits γ-secretase activity.

25. A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising adminstering a therapeutically effective amount of a compound as defined in claim 1.

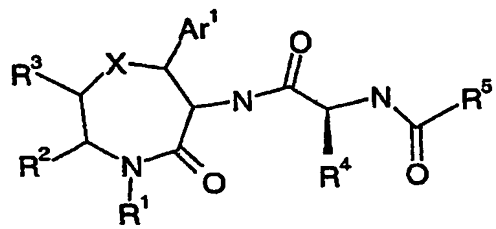
26. A method for the treatment or prophylaxis of Alzheimer's disease, or Down's Syndrome comprising adminstering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt as claimed in any one of claims 1 to 21.

27. A pharmaceutical composition comprisisng a compound of formula (I), as defined in any one of claims 1 to 21, together with at least one phamraceutically acceptable carrier, diluent or excipent.

ABSTRACT

NOVEL BENZOTHIAZEPINES AND USES THEREOF

This invention relates to novel compounds having the structual diagram (I)



to their pharmaceutical compositions and to their methods of use. These novel compounds inhibit γ secretase and thereby inhibit the production of amyloid β protein, thereby acting to prevent the formation of neurological deposits of amyloid protein. The present invention relates to the treatment of neurological disorders related to amyloid β protein production such as Alzheimer's disease.